ME

(19) Europäisch s Pat ntamt
European Patent Office
Office europé n d s brevets

(11) Publication number: 0 361 680 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: 13.07.94

(51) Int. Cl.5: A61K 9/46, A61K 31/485, A61K 9/16

(21) Application number: 89308659.5

(22) Date of filing: 25.08.89

(54) Morphine-containing composition.

(30) Priority: 26.08.88 GB 8820327

(43) Date of publication of application:
04.04.90 Bulletin 90/14

(45) Publication of the grant of the patent:
13.07.94 Bulletin 94/28

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 074 105
EP-A- 0 190 689
EP-A- 0 203 768
FR-A- 2 013 552

PATENT ABSTRACTS OF JAPAN, vol. 10, no. 230 (C-365)(2286), 9 August 1986; & JP-A-6165823 (Kao Corp.)

(73) Proprietor: RHONE-POULENC RORER LIMITED
RPR House,
St. Leonards Road
Eastbourne, East Sussex BN21 3YG(GB)

(72) Inventor: Michell, Robin Paul
c/o May & Baker Limited
Dagenham Essex, RM10 7XS(GB)

(74) Representative: Bentham, Stephen et al
J.A. KEMP & CO.
14 South Square
Gray's Inn
London WC1R 5LX (GB)

EP 0 361 680 B1

Description

This invention relates to a novel pharmaceutical formulation and a process for its preparation.

Effervescent formulations are a particularly acceptable way of presenting many drugs to patients, especially if they need to be taken on a long term or regular basis.

Effervescence is the evolution of bubbles from a liquid, for example as a result of chemical action. In the case of pharmaceutical products this gas is normally carbon dioxide which is liberated by the reaction between a physiologically acceptable acid (e.g. citric, tartaric or malic acid) and a source of carbonate (such as sodium carbonate, sodium bicarbonate or a mixture thereof). It is convenient for these basic and acidic components of the "effervescent couple" to be separately granulated (e.g. by wet granulation, preferably in water), dried and then combined prior to or during packaging. The resultant mixture will then produce effervescence on being added to water.

Morphine is a drug which is often taken on a long term or regular basis and although it is available in a number of forms it has so far not been produced in an effervescent formulation.

EP-A- 0 190 689 discloses a method for producing a foaming composition by mixing together acidic and basic components, one of which also contains an active ingredient.

It is known that morphine is normally degraded by oxidation, promoted by a wide variety of circumstances, and that this occurs more readily in basic media. It would therefore appear obvious to incorporate the morphine into the acid component of the effervescent couple. A further advantage would appear to be that ascorbic acid could be incorporated in this acidic mixture as an antioxidant. When such a composition is made up however, it is found that a significant decrease in activity occurs during storage. Analysis shows that this is due to esterification of phenolic groups in the morphine by the acids.

It has surprisingly been found that incorporation of the morphine in the basic component of an effervescent couple does not lead to any substantial loss in activity, even when it is in contact with granules of the acidic component.

Thus the invention provides a granule for inclusion in an effervescent formulation comprising morphine or a pharmaceutically acceptable salt thereof and the basic component of an effervescent couple.

The basic component is preferably sodium carbonate, sodium bicarbonate or a mixture thereof.

The invention also provides an effervescent formulation comprising such granules.

The morphine is generally present in the form of a pharmaceutically acceptable salt, for example morphine hydrochloride or morphine sulphate.

The stability of the effervescent morphine formulation according to the invention allows it to be readily incorporated into unit dosage forms, especially sachets. These typically contain 5, 10 or 30mg of morphine sulphate and dissolution of the contents of one or two of them in water allows a number of doses of from 5 to 60mg - or more if required - to be conveniently prepared and taken.

Granules containing the basic component of the couple are typically prepared by dry mixing morphine sulphate, sodium bicarbonate and a solid binder material such as polyvinylpyrrolidone (PVP), granulation in an aqueous solution of binder (again typically PVP in a concentration of for example 20% w/w), drying and milling. The PVP used can be for example PVP K30. Granulation may be performed in a high speed granulator (e.g. a Fielder or Diosna granulator), drying in a fluid bed drier (e.g. as manufactured by Glatt or Aeromatic) or an oven, typically at 60 °C, and milling on a 2mm screen (e.g. Glatt Quicksieve).

The relative amounts of solid and aqueous binder (PVP) depend - as normal in granulation processes - on the scale of the process and can be easily determined by those skilled in the art.

Acidic granules can be prepared in a similar fashion starting from, for example, tartaric acid and/or citric acid and binder (PVP) and can also include ascorbic acid.

The final product can then be obtained by mixing these two granular materials with extragranular components such as sodium carbonate, sweeteners (e.g. aspartame) and flavourings (e.g. Lemon Juice Flav-O-Lok). This can be carried out in a blender, such as an Oblicone cone blender, a Turbula mixer or a Flow-bin type blender.

The following Examples illustrate the invention:

Example 1

Basic granules were formed by dry-mixing morphine sulphate B.P. (17.5g) sodium bicarbonate B.P. (2813g) and solid PVP, granulating with an aqueous solution of PVP (PVP K30, total weight of PVP used 63.7g), drying at 60 °C and passing through a 2mm screen.

Acidic granules were prepared in a similar manner using tartaric acid B.P. (2013g), anhydrous citric acid B.P. (1224g) and solid and aqueous PVP (total weight 30.1g).

The two batches of granules were then mixed together along with sodium carbonate BPC (7 aspartame ('Nutrasweet', 105g) and 'Lemon Juice Flav-O-Lok 610406E' flavouring (28g), to proc product having the following overall composition (w/w):-

Morphine sulphate	0.25%
PVP	1.35%
Sodium bicarbonate	40.2 %
Tartaric acid	28.75%
Citric acid	17.5 %
Sodium carbonate	10.05%
Aspartame	1.5 %
Flav-O-Lok	0.4 %

This was then filled into sachets, each of which nominally contained 5mg of morphine sulphate sachet contents approximately 2g)

Examples 2 and 3

Sachets nominally containing 10 and 30mg of morphine sulphate in a total weight of 2g were pre in a similar manner - the appropriate weight of sodium bicarbonate being replaced by morphine sulph the initial basic mix.

Reference Example

An unsatisfactory (unstable) composition was prepared in a similar manner by mixing acidic gra made from morphine sulphate (17.5g), citric acid (1224g), tartaric acid (2010g) and PVP (30.2g) and granules made from sodium bicarbonate (2813g) and PVP (64.3g) with sodium carbonate (70: aspartame (105.5g) and Flav-o-Lok (28.1g).

The relative stability of the formulation according to the invention is shown in Table I. Samples prepared in a similar manner to those in Example 1 and the Reference Example above.

Table I

Conditions	morphine sulphate content (mg/sachet)	
	morphine in acidic granules	morphine in basic granules
Initial	4.97	5.04
one month at:- room temperature		
22 • C/55%r.h.*	4.69 (94.4%)	4.93 (97.8%)
37 • C/80%r.h.	4.52 (90.9%)	4.95 (98.2%)
45 • C/ambient humidity	4.04 (81.3%)	4.87 (96.6%)

* r.h. = relative humidity

Similar samples with morphine in the basic granules were also tested as shown in Table II.

Table II

test conditions	% morphine still present after		
	3 months	6 months	12 months
22 • C/55%r.h.	98.4	97.4	95.6
37 • C/ambient humidity	96.0	95.4	92.7
37 • C/80%r.h.	100.0	98.2	94.6
45 • C/ambient humidity	94.8	96.0	not tested

Samples containing 30mg morphine sulphate in the basic granules showed no significant loss in ac material content under any of the conditions listed above.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A granule for inclusion in an effervescent formulation comprising morphine or a pharmaceutic acceptable salt thereof and the basic component of an effervescent couple.

2. A granule according to claim 1, wherein the basic component is sodium carbonate, sodium bicarbon or a mixture thereof.

3. A granule according to claim 1 or 2, which comprises a solid binder material.

4. A granule according to claim 3, wherein the solid binder material is polyvinylpyrrolidone.

5. A granule according to any one of the preceding claims in which the morphine is present as morph sulphate.

6. An effervescent formulation which comprises granules according to any one of claims 1 to 5.

7. An effervescent formulation according to claim 6, which further comprises acidic granules.

8. An effervescent formulation according to claim 7, in which the acid granules comprise tartaric or ci acid and a binder.

Claims for the following Contracting States : GR, ES

1. A process for producing granules for inclusion in an effervescent formulation comprising formulati morphine or a pharmaceutically acceptable salt thereof and the basic component of an effervesc couple.

2. A process according to claim 1, wherein the basic component is sodium carbonate, sodium bicarbon or a mixture thereof.

3. A process according to claim 1 or 2, which further comprises formulating a solid binder material.

4. A process according to claim 3, wherein the solid binder material is polyvinylpyrrolidone.

5. A process according to any one of the preceding claims in which the morphine is present as morphi sulphate.

6. A process for producing an effervescent formulation which comprises formulating granules according any one of claims 1 to 5.

7. A process according to claim 6 which further comprises formulating acidic granules.

8. A process according to claim 7 in which the acidic granules comprise tartaric or citric acid and binder.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Granulat zum Einbau in eine sprudelnde Zubereitung mit Morphin oder einem pharmazeutisch akzept blen Salz desselben und der Grundkomponente eines Brausepaares.

2. Granulat nach Anspruch 1, wobei die Grundkomponente aus Natriumcarbonat, Natriumbicarbonat od einer Mischung derselben besteht.

3. Granulat nach Anspruch 1 oder 2, umfassend ein festes Bindemittel.

4. Granulat nach Anspruch 3, wobei das feste Bindemittel aus Polyvinylpyrrolidon besteht.

5. Granulat nach einem der vorhergehenden Ansprüche, wobei das Morphin als Morphinsulfat vorhanden ist.

6. Sprudelnde Zubereitung, umfassend ein Granulat nach einem der Ansprüche 1 bis 5.

7. Sprudelnde Zubereitung nach Anspruch 6, wobei zusätzlich ein saures Granulat enthalten ist.

8. Sprudelnde Zubereitung nach Anspruch 7, wobei das saure Granulat Wein- oder Zitronensäure und ein Bindemittel umfaßt.

Patentansprüche für folgende Vertragsstaaten : GR, ES

1. Verfahren zur Herstellung eines Granulats zum Einbau in eine sprudelnde Zubereitung durch Vereinigen von Morphin oder eines pharmazeutisch akzeptablen Salzes desselben mit der Grundkomponente eines Brausepaares.

2. Verfahren nach Anspruch 1, wobei die Grundkomponente aus Natriumcarbonat, Natriumbicarbonat oder einer Mischung derselben besteht.

3. Verfahren nach Anspruch 1 oder 2, ferner umfassend ein festes Bindemittel.

4. Verfahren nach Anspruch 3, wobei das feste Bindemittel aus Polyvinylpyrrolidon besteht.

5. Verfahren nach einem der vorhergehenden Ansprüche, wobei das Morphin als Morphinsulfat vorhanden ist.

6. Verfahren zur Herstellung einer sprudelnden Zubereitung durch Formulieren eines Granulats nach einem der Ansprüche 1 bis 5.

7. Verfahren nach Anspruch 6, bei welchem ein saures Granulat mitformuliert wird.

8. Verfahren nach Anspruch 7, bei welchem das saure Granulat Wein- oder Zitronensäure und ein Bindmittel umfaßt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Granulé pour l'incorporation dans une formulation effervescente comprenant de la morphine ou un sel pharmaceutiquement acceptable de celle-ci et les composants basiques d'un mélange effervescent.

2. Granulé selon la revendication 1, dans lequel le composant basique est le carbonate de sodium, le bicarbonate de sodium ou un mélange de ceux-ci.

3. Granulé selon la revendication 1 ou 2, lequel comprend une substance liante solide.

4. Granulé selon la revendication 3, dans lequel la substance liante solide est la polyvinylpyrrolidone.

5. Granulé selon l'une quelconque des revendications précédentes, dans lequel la morphine est présente sous forme de sulfate de morphine.

6. Formulation effervescente, laquelle comprend des granulés selon l'une quelconque des revendications 1 à 5.

7. Formulation effervescente selon la revendication 6, laquelle comprend en outre des granulés acides.

8. Formulation effervescente selon la r vendication 7, dans laquelle les granulés acides comprennent l'acide tartrique ou l'acide citrique et un liant.

Revendications pour les Etats contractants suivants : GR, ES

1. Procédé de fabrication de granulés pour une incorporation dans une formulation effervescente, comprenant la mise en formulation de la morphine ou un sel pharmaceutiquement acceptable de celle-ci et du composant basique d'un couple effervescent.

2. Procédé selon la revendication 1, dans lequel le composant basique est le carbonate de sodium , le bicarbonate de sodium ou un mélange de ceux-ci.

3. Procédé selon la revendication 1 ou 2, lequel comprend en outre la mise en formulation d'une substance liante solide.

4. Procédé selon la revendication 3, dans lequel la substance liante solide est la polyvinylpyrrolidone.

5. Procédé selon l'une quelconque des revendications précédentes, dans lequel la morphine est présente sous forme de sulfate de morphine.

6. Procédé de préparation d'une formulation effervescente, lequel comprend la formulation de granulés selon l'une quelconque des revendications 1 à 5.

7. Procédé selon la revendication 6, lequel comprend en outre la mise en formulation de granulés acides.

8. Procédé selon la revendication 7, dans lequel les granulés acides comprennent l'acide tartrique ou l'acide citrique et un liant.